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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,729	06/12/2001	Jay M. Short	09010-003005	6449

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,729	SHORT ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-92* is/are pending in the application.

4a) Of the above claim(s) *1-41 and 56-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-92 are currently pending in this application. Claims 42-55 are now under consideration. Claims 1-41, 56-92 remain withdrawn from consideration as being drawn to non-elected subject matter.

Election/Restrictions

Applicant's election of Group IV, claims 42-55 in Paper No. 20 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Method of generating variants of a *Hermitage maritima* enzyme having CMC-cellulase activity".

Priority

Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 08/518,615 filed on 08/23/1995, now US 5,962,258, 0/951,889 filed on 10/16/1997, now US 6,008,032, 09/472,857 filed on 12/27/1999, now US 6,245,647. However,

Examiner has not granted the above priority dates for claims 43-55 as they do not support in the priority documents.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that figure 5 lacks SEQ ID NO either in the figure or in the figure description. See particularly 37 CFR 1.821(d).

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 42 (claims 43-55 dependent thereon) is indefinite in the recitation of "obtaining a nucleic acid comprising a sequence as set forth in SEQ ID NO:1, sequences substantially identical thereto, sequences complementary thereto, fragments comprising at least 30 consecutive nucleotides thereof, and fragments comprising at least 30 consecutive nucleotides of the sequences complementary to SEQ ID NO: 1" for the following reasons.

The claim is indefinite in the recitation of "sequences complementary thereto" as it is unclear if the term "thereto" refers to SEQ ID NO:1 or "the substantially identical" sequence.

The claim is also indefinite in the recitation of "fragments comprising... thereof" as it is unclear which nucleic acids are being referred to by the term "thereof". Since the term "substantially identical" in regard to nucleic acid sequences has been defined in the specification (page 12), the claim will be interpreted as being drawn to a method of generating a variant comprising obtaining a nucleic acid selected from the group consisting of (a) the polynucleotide of SEQ ID NO: 1, (b) any polynucleotide having at least 50% sequence identity to any fragment of the polynucleotide of SEQ ID NO: 1, (c) any polynucleotide which is completely complementary to (a) or (b), (d) a fragment of at least 30 consecutive nucleotides of (a), (b), or (c), (h) a fragment of at least 30 consecutive nucleotides of the sequences complementary to SEQ ID NO: 1. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method for generating a variant comprising obtaining (1) a genus of nucleic acids of <u>any function</u> having at least 50% sequence identity to the polynucleotide with SEQ ID NO: 1, (2) a genus of nucleic acids which are completely

complementary to (1), (3) a genus of nucleic acid fragments of at least 30 consecutive nucleotides of (1), (2), or (3). While the specification discloses the polynucleotide of SEQ ID NO: 1 and the corresponding polypeptide, as well as a method for generating polynucleotide/polypeptide variants of the polynucleotide/polypeptide of SEQ ID NO: 1 which still retain cellulase activity, the specification fails to disclose a method of creating variants, as defined in the specification, using (1) nucleic acids of any function having at least 50% sequence identity to any fragment of the polynucleotide of SEQ ID NO: 1 or (2) nucleic acids which are fragments of (1). It is noted that the term "variant" has been defined in the specification (page 13-14) as "polynucleotide or polypeptide modified at one or more base pairs, codons, introns, exons, or amino acid residues yet still retain the biological activity of a CMC-cellulase". The specification does not disclose the critical structural elements required in a nucleic acid having at least 50% sequence identity to any fragment of the polynucleotide of SEQ ID NO: 1 to encode a polypeptide which has CMC-cellulase activity, nor does it describe which fragments of such nucleic acid would encode a polypeptide having CMC-cellulase activity.

While one could argue that the nucleic acids required to practice the claimed method are adequately described since one can isolate nucleic acids of similar function by sequence comparison using the polynucleotides/polypeptides of the instant application or the prior art, the state of the art teaches that sequence comparison alone should not be used to determine function and that small structural changes can drastically change function. Bork (Genome Research, 10:398-400, 2000;) teaches protein function is context dependent, and both molecular and cellular aspects must be considered. Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl

decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995; cited in the IDS) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998; cited in the IDS) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a single species of the genera of nucleic acids required to practice the invention which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of the claimed method. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

Claims 42-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for generating variants comprising obtaining a nucleic acid comprising the polynucleotide of SEQ ID NO: 1 and modify such nucleic acid as encompassed by the claims, does not reasonably provide enablement for a method of generating variants comprising obtaining any nucleic acid which is at least 50% sequence identical to any fragment of the polynucleotide of SEQ ID NO: 1 and modify such nucleic acid according to the claims. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims as described above is not commensurate with the enablement provided in regard to the large number of unknown polynucleotides required to practice the claimed method. As indicated above, the specification describes a method of generating variants of the polynucleotide/polypeptide of SEQ ID NO: 1 which still retain CMC-cellulase activity (page 13-14), but the specification fails to disclose a method of creating variants, as defined in the specification, using (1) nucleic acids of any function having at least 50% sequence identity to any fragment of the polynucleotide of SEQ ID NO:1 or (2) nucleic acids which are fragments of (1). Since the variant obtained by the method as described in the specification still retains CMC-cellulase activity, it is unclear how one of skill in the art can practice the claimed method with polynucleotides of any function as described above. In addition, the specification does not disclose the critical structural elements required in any nucleic acid to encode a polypeptide which has CMC-cellulase activity, nor does it describe which fragments of such nucleic acid would encode a polypeptide having CMC-cellulase activity. Furthermore, as discussed above, the state of the art teaches that isolation of polynucleotides of similar function is unpredictable, as evidenced by Bork, Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al.

Since structure determines function, one of skill in the art would require some knowledge or guidance as to how structure correlates with function to isolate the polynucleotides required to practice the claimed method. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to maintain the desired function, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to screen and isolate those polynucleotides, as encompassed by the claims, which encode polypeptides of α-galactosidase activity, to practice the claimed method. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bronnenmeier et al. and Short (US Patent 5,939,250). Claims 42-55 are drawn to a method for generating variants

comprising obtaining a nucleic acid comprising the polynucleotide of SEQ ID NO: 1 and modify such nucleic acid using techniques such as "error-prone PCR", "shuffling", "oligonucleotide-directed mutagenesis", "assembly PCR", "sexual PCR mutagenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis", "exponential ensemble mutagenesis", and "site-specific mutagenesis".

Bronnenmeier et al. teach the purification of cellulase enzymes from *T.maritima*. However, Bronnenmeier et al. do not teach the polynucleotide sequence encoding said enzymes. As the source of enzymes in the reference and in the instant application are one and the same, Examiner takes the position that the enzymes in the reference are encoded by a nucleic acid that is substantially identical to SEQ ID NO:1.

Short teaches a number of known techniques for directed mutagenesis for the development of modified enzymes with particularly desired properties that are absent or less pronounced in the wild-type enzyme, such as stability to heat or organic solvents. Short specifically teaches "error-prone PCR", "shuffling", "oligonucleotide-directed mutagenesis", "assembly PCR", "sexual PCR mutagenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis", "exponential ensemble mutagenesis", and "site-specific mutagenesis".

With the two references in hand it would have been obvious to one of ordinary skill in the art to obtain the amino acid sequences of the enzymes purified by Bronnenmeier et al. and deduce their polynucleotide sequence and use such polynucleotides to obtain variants of the same. One of ordinary skill in the art at the time of filing would have been motivated to modify the nucleic acid sequence encoding the cellulase of Bronnenmeier et al. using each of the methods taught by Short, including "error-prone PCR", "shuffling", "oligonucleotide-directed mutagenesis", "assembly PCR", "sexual PCR mutagenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis", "exponential ensemble mutagenesis", and

"site-specific mutagenesis" in order to modify the amino acid sequence of the CMC-cellulase such that the enzyme has a increased cellulase activity relative to the wild-type enzyme. One of ordinary skill in the art at the time of filing would have a reasonable expectation of success because of the high level of knowledge in the field of nucleic acid mutagenesis and the teachings of Bronnenmeier et al. who successfully purify the cellulase enzyme from *T.maritima* and Short et al. provide ample number of techniques for modifying polynucleotide sequences. Thus Bronnenmeier et al. and Short make obvious claims 42-55 drawn methods of generating a variant comprising obtaining a nucleic acid comprising a sequence substantially identical to SEQ ID NO: 1 and modifying, deleting or adding one or more nucleotides in said sequence to another nucleotide, wherein the modifications are introduced by error-prone PCR (claims 42-44), shuffling (claims 42, 43 and 45), oligonucleotide-directed mutagenesis (claims 42, 43 and 46), assembly PCR (claims 42, 43 and 47), sexual PCR mutagenesis (claims 42, 43 and 48), *in vivo* mutagenesis (claims 42, 43 and 49), cassette mutagenesis (claims 42, 43 and 50), recursive ensemble mutagenesis (claims 42, 43 and 51), exponential ensemble mutagenesis (claims 42, 43 and 52), or site-specific mutagenesis (claims 42, 43 and 53).

Claims 42, 43, 54, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bronnenmeier et al. in view of Short (US Patent 6,479,258).

Bronnenmeier et al. is discussed above. Bronnenmeier et al. do not use the methods of mutagenesis specifically recited in Claims 44-53 to produce the mutant CMC-cellulases.

Short teaches a number of known techniques for non-stochastic methods of directed mutagenesis for the development of modified enzymes with particularly desired properties that are absent or less pronounced in the wild-type enzyme, such as stability to heat or organic solvents. Short specifically teaches "gene reassembly", and "gene site saturated mutagenesis".

One of ordinary skill in the art at the time of filing would have been motivated to modify the nucleic acid sequence encoding the cellulase of Bronnenmeier et al. using the methods taught by Short, including "gene reassembly", and "gene site saturated mutagenesis" in order to modify the amino acid sequence of the CMC-cellulase such that the enzyme has a increased cellulase activity relative to the wild-type enzyme. One of ordinary skill in the art at the time of filing would have a reasonable expectation of success because of the high level of knowledge in the field of nucleic acid mutagenesis and the teachings of Bronnenmeier et al. who successfully purify cellulase from *T.maritima* which can be used to deduce the encoding nucleic acid. Thus Bronnenmeier et al. and Short make obvious claims 42, 43, 54, and 55 drawn methods of generating a variant comprising obtaining a nucleic acid comprising a sequence substantially identical to SEQ ID NO: 1 and modifying, deleting or adding one or more nucleotides in said sequence to another nucleotide, wherein the modifications are introduced by gene reassembly (claims 42, 43 and 54), or gene site saturated mutagenesis (claims 42, 43 and 55).

Conclusion

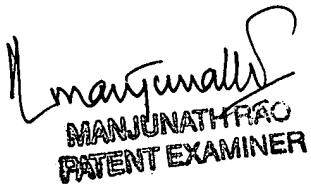
None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone

numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.



Manjunath N. Rao
June 20, 2003